

enced attorneys who have at their disposal the best in the medical community who are happy, for a price, to step forward and proclaim the “innocence” of the unfortunate doctor.

I prefer to believe that the medical community and the plaintiffs bar are united in the common ideal of providing competent medical care and thus holding responsible

those who engage in conduct below the standard of care. I have always viewed the role of the attorney as trying to prevent injury much as the medical community strives to prevent illness. Medical malpractice is inevitable, but practicing within the standard of care offers more than a safe harbor for medical negligence claims, it offers protection for your patients.

Placebo-controlled trials: good science or medical neglect?

The placebo-controlled clinical trial has a long history of being the standard for clinical investigations of new drugs. By blindly and randomly allocating similar patients to a control group that receives a placebo and an experimental group, investigators can ensure that any possible placebo effect will be minimized in the final statistical analysis. Although this approach to clinical research is scientifically sound, ethical concerns arise in some cases that outweigh the benefits of this protocol design. Even though patients may be advised of the likelihood of being placed in a placebo group and that the intent of the clinical trial is research, not medical care, they often hope for some level of treatment. More importantly, when effective treatments exist, research participants who have progressive, burdensome disease should be given standard treatment as the control agent.

Using a recent example of a clinical trial of a new drug for treating rheumatoid arthritis, we argue that research participants who have burdensome, progressive disease should not be exposed to the risks of placebo-controlled trials. Historical controls and active controls may need more people in a particular trial but do not deprive patients of approved treatment. We propose several guidelines for considering the ethical use of placebo controls in clinical trials and call on research regulatory agencies to standardize their recommendations.

A NEW DRUG FOR TREATING RHEUMATOID ARTHRITIS

In August 1998, the Arthritis Advisory Committee for the US Food and Drug Administration unanimously recommended approval of a new drug for the treatment of rheumatoid arthritis.¹ The new compound won approval from the advisory panel because of its efficacy in treating both

the symptoms and the progression of this disease and because of its favorable profile related to some side effects. In the phase 3 study that led to approval, 482 patients with active rheumatoid arthritis were enrolled in a 1-year, multicenter, randomized, double-blind, parallel-group study that compared the new drug with methotrexate or placebo.² Symptoms decreased in 41% of those who were given the study drug. Approximately the same percentage of patients given methotrexate had subjective improvement, but only 19% of those given placebo reported symptomatic relief. Structural damage to bone and cartilage occurred four times faster in the group taking placebo than in either of the groups that were given active treatment.

This medical breakthrough represents a major step in the medical treatment of a large number of people with rheumatoid arthritis. Of equal importance, however, is that 118 of the 482 subjects studied were given a placebo

Summary points

- The use of placebo controls in clinical research that involves patients who have an active disease for which there is approved treatment is ethically questionable and may represent substandard care
- The use of active or historical controls in clinical research may address these ethical questions
- Federal guidelines say that a condition of clinical equipoise should exist before a placebo-control study is started. Although this is a reasonable guideline, sponsors or investigators may be ignoring it
- Research participants with active disease are likely to believe they will possibly benefit from taking part in trials. This therapeutic misconception may not be obviated by an informed consent form

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for 1 year and closely monitored while an irreversible disease process that could have been mediated by an approved drug was allowed to advance. For this unfortunate group, the wisdom of placebo controls is unclear.

THERAPEUTIC TRIALS AND THERAPEUTIC MISCONCEPTIONS

Clinical trials frequently recruit volunteers with active disease or conditions for which treatment is normally prescribed. Regardless of disclaimers made during the consent process, such participants often hope that the experimental therapy will improve their condition.^{3,4} This discrepancy between a subject's hope for a cure and the experimental objectives of the research protocol has been termed the "therapeutic misconception" and explains, in part, why the standards for the protection of and disclosure to research subjects are higher than those for patient consent to medical care.⁵⁻⁹ These standards need sponsors and institutional review boards to exhaust all possibilities for alternative research designs before a placebo-controlled trial is conducted with participants who have active disease for which approved treatment exists. If patients with rheumatoid arthritis were given the wrong medicine by a physician and their medical condition declined, they would be justified in making malpractice claims. Why, when the ethical requirements for protection and disclosure are appropriately more stringent for clinical research, is such a study design considered scientifically justified? Even if the demands of science argue in favor of such a protocol, the canons of ethics forbid it.

CONFLICTS IN ETHICS AND REGULATIONS

The Nuremberg Code, the Declaration of Helsinki, and the Belmont Report have all provided the framework for the current Office for Protection from Research Risk (OPRR) guidebook that informs institutional review boards in their assessments of human subjects protocols.¹⁰⁻¹³ All of these documents base their guidance on protecting human participants. At times, however, federal regulations may conflict with the ethical guidelines provided by the OPRR.^{13,14}

Although ethical guidelines do not rule out placebo-controlled studies, they emphasize the well-being of participants and the need for scrutiny by an institutional review board.^{12,13} Risks of "serious impairment" require extraordinary justification, and placebo controls are not to be used if there is evidence of the efficacy of another treatment or "good evidence" that the experimental therapy is effective. These guidelines call on institutional review

boards to perform a careful risk-benefit analysis when considering whether to allow a placebo-controlled trial. In addition, the investigator must be able to "honestly . . . state" a condition of "clinical equipoise."¹³ However, investigators are advised that "the control treatment must be the best standard therapy currently available."

A possible reason for the persistence of placebo controls in many drug trials is that research that is privately sponsored must answer to the Food and Drug Administration to get approval for new drugs. Placebo-controlled clinical trials still seem to be required for the Food and Drug Administration to approve the use of a new drug.^{3,13,14}

FOOD AND DRUG ADMINISTRATION GUIDANCE

The Food and Drug Administration addresses the ethical concerns of using placebo controls by suggesting that such trials may be short, should provide for withdrawal if a participant's condition worsens, and should frequently monitor the progression of the disease. Investigators are warned that the quest for statistically significant differences between placebo effects and experimental therapy does not justify exposing participants to "documented serious risk."¹⁵ These guidelines stop short of defining serious risk, leaving that determination to sponsors and institutional review boards.

Yet, the Food and Drug Administration has historically withheld its approval of some drugs when placebo controls were not used.^{3,14,16} Three defenses for this decision have been advanced.^{16,17} First, a large number of participants is needed to show significant difference in the effects of two drugs that mimic each other. Second, trials that are intended to show no significant differences between two therapies—that is, that two drugs are therapeutically equivalent—could reduce the emphasis on strict scientific conduct. Third, equivalence trials assume that the active control was effective specifically in the study in which it was used and, thus, would have been superior to a placebo had one been used. We will address each of these concerns separately.

Number of subjects

If a new drug is being compared with an existing therapy that is known to be effective, the sponsor will either have to settle for showing equivalency or, in addition, a more favorable profile of side effects. Two medications with similar effects may show significant differences when compared with a placebo but not when compared with each other. Although sponsors may balk at the prospect of lengthy trials with a large number of participants, the

equivalence-versus-superiority argument is a marketing concern and does not ethically justify exposing participants to an avoidable risk.

Incentives for study excellence

The second issue is an ethical rather than a statistical one. Equivalence trials are intended to show the comparability of new and existing therapies, and anything that obscures differences (favorable or unfavorable) between the two would help support this claim. Some have argued that this provides an incentive for investigators to be lax in screening potential participants for inclusion, assessing outcomes, and monitoring compliance. This behavior jeopardizes scientific integrity.¹⁸

Consistency of active control effect

The third concern, about active controls, is that showing equivalence to an active control assumes that the control (drug) would be superior to a placebo had one been used in that particular trial. Approved drugs, by definition, have shown efficacy as part of the Food and Drug Administration approval process. If an approved drug with a historical profile is used as the control for an investigation involving a disease with objective measures of progression or remission, then it is unnecessary to make assumptions regarding the drug's efficacy in the current trial.

PLACEBO-CONTROL GUIDELINES

We propose that definable conditions exist that should be addressed before placebo-controlled trials are permitted to proceed. The assessment of these clinical conditions is grounded in the ethical requirements outlined in the Belmont Report¹² and reflects the current guidance of the OPRR guidelines. For the approval of placebo controls in phase 2, 3, and 4 trials, the following questions should be considered:

- Do participants have a disease or condition for which treatment is available, normally prescribed, and of known efficacy?
- Will lack of treatment likely result in progression of the disease or condition or the infliction of pain or suffering during the trial?
- If the disease or condition progresses, is this likely to be reversible?
- If the disease process is irreversible, how great is the burden of this progression, and how likely is existing treatment to resolve or reduce this burden?
- Is there substantial evidence that the experimental treatment is of therapeutic benefit?

The answers to these questions should serve to guide institutional review boards in determining whether a placebo-control group is justified. Complete ethical accountability requires that sponsors, institutions, and investigators accept responsibility for subjects who suffer harm because they were given a placebo rather than an available standard therapy. A signed consent form should not shield investigators from claims of malpractice if standard therapy for a condition was intentionally withheld and the subject suffered irreversible harm.

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